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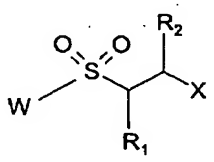
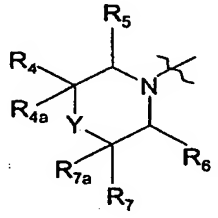
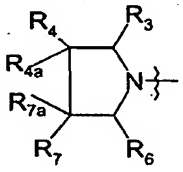
(54) Title: HYDROXAMIC ACID DERIVATIVES AS PROTEINASE INHIBITORS



(I)



(IIIA)



(IIIB)

(57) Abstract

Compounds of formula (I) are matrix metalloproteinase inhibitors wherein X represents a carboxylic acid group –COOH, or a hydroxamic acid group –CONHOH; R_2 represents a radical of the formula (II): R_3–$(ALK)_m$–$(Q)_p$–$(ALK)_n$–, and W represents a cyclic amino radical of formula (IIIA) or (IIIB).

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Hydroxamic Acid Derivatives as Proteinase Inhibitors.

This invention relates to novel hydroxamic acid and carboxylic acid derivatives which are inhibitors of matrix metalloproteinases to pharmaceutical compositions comprising such compounds and to their use in the treatment of diseases and conditions responsive to modulation of matrix metalloproteinase activity.

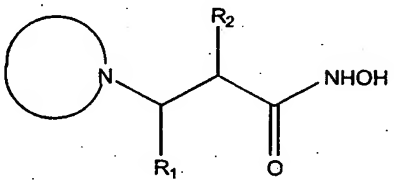
Background to the Invention

The matrix metalloproteinases (MMPs) are a family of enzymes including interstitial collagenase, neutrophil collagenase, collagenase-3, 72kDa gelatinase, 92kDa gelatinase, stromelysin-1, stromelysin-2, stromelysin-3, matrilysin, macrophage metalloelastase, membrane-type metalloproteinase-1 and membrane-type metalloproteinase-2. These enzymes share a common zinc-containing catalytic domain and a pro-sequence which maintains latency. A wide range of cells and tissues can express MMPs in response to activation by inflammatory stimuli such as interleukin-1 or tumour necrosis factor-α (TNF-α). Different stimuli can induce overlapping yet distinct repertoires of MMPs and different cell types can respond to the same stimuli by expression of distinct combinations of MMPs. MMPs can degrade the protein components of extracellular matrix such as collagens, vitronectin and elastin, and have recently been shown to process membrane proteins such as pro-TNF-α to release soluble TNF-α. MMPs are thought to play a central role in the pathology of inflammatory diseases such as rheumatoid arthritis as well as in the growth and metastasis of tumours.

Compounds which have the property of inhibiting the action of MMPs are thought to be potentially useful for the treatment or prophylaxis of conditions involving such tissue breakdown, for example rheumatoid arthritis, osteoarthritis, osteopenias such as osteoporosis, periodontitis, gingivitis, corneal epidermal venous, diabetic or gastric ulceration, ulcerative colitis, Crohn's disease, pressure sores, and tumour metastasis, invasion and growth. MMP inhibitors are also of potential value in the

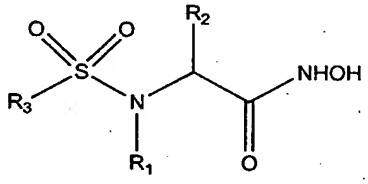
treatment of neuroinflammatory disorders, including those involving myelin degradation, for example multiple sclerosis, as well as in the management of angiogenesis dependent diseases which include arthritic conditions and solid tumour growth as well as psoriasis, proliferative retinopathies, neovascular glaucoma, ocular tumours, angiofibromas and hemangiomas, cardiac and cerebral infarction, and wound healing.

A known class of collagenase inhibitors is represented by those disclosed in EP-A-0574758 (Roche), EP-A-0684240 (Roche), and WO 95/33731 (Roche). In general, the compounds disclosed in those publications may be represented by the structural formula (IA):

(IA) 

in which R_1, R_2 and the N-containing ring are variable in accordance with the specific disclosures of the publications.

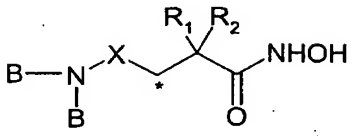
Another known class of MMP inhibitors is represented by those disclosed in EP-A-0606046 (Ciba-Geigy) WO 96/00214 (Ciba-Geigy), WO 95/35275 (British Biotech) and WO 95/35276 (British Biotech), which in general may be represented by the structural formula (IB):

(IB) 

in which R_1, R_2 and and R_3 are variable in accordance with the specific disclosures of the publications.

WO 99/24399 (Darwin Discovery Ltd), published 20 May 1999, discloses MMP

inhibitors *inter alia* of structural formula (IC)

(IC) 

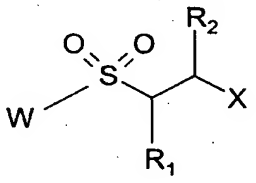
wherein X is $-SO_2-$ or -SO-, and R_1, R_2 and each B is as defined in the document.

Brief Description of the Invention

The present invention makes available a new class of inhibitors of MMPs which, as a result of that activity, are useful in the management of diseases or disorders associated with over production of or over responsiveness to MMPs. The compounds of the invention differ in structure from those of WO 99/24399 *inter alia* in that the methylene group equivalent to that marked with an asterisk in formula (IC) is substituted in the present compounds.

Detailed description of the invention

According to the present invention there is provided a compound of formula (I)

(I) 

wherein

X represents a carboxylic acid group -COOH, or a hydroxamic acid group -CONHOH;

R_2 represents a radical of formula (II)

$$R_3\text{-}(ALK)_m\text{-}(Q)_p\text{-}(ALK)_n\text{-} \qquad (II)$$

wherein

R_3 represents hydrogen or an optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted aryl, or optionally substituted heterocyclic ring having 5 or 6 ring members,

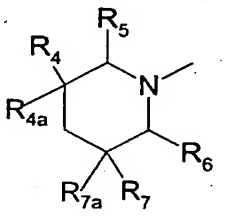
each ALK independently represents an optionally substituted divalent C_1-C_3 alkylene radical,

Q represents -O-, -S-, -S(O)-, -S(O_2)-, -C(O)O-, -OC(O)- or -N(R_9)- wherein R_9 is hydrogen, C_1-C_6alkyl, or C_1-C_6alkoxy, and

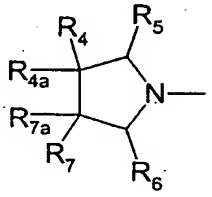
m, n and p are independently 0 or 1;

R_1 represents a radical of formula (II) as defined for R_2, except that R_1 is not hydrogen;

W represents a cyclic amino radical of formula (IIIA) or (IIIB):



(IIIA)



(IIIB)

wherein

Y represents -O-, -S-, -S(O)-, -S(O_2)-, -N(R_8)-, -(CH(R_8))-, or -(C=N-R_8)- wherein R_8 is a radical of formula (II) as defined in relation to R_2; and

(i) R_4, R_5, R_6 and R_7 each independently represents a radical of formula (II) as defined in relation to R_2, and R_{4a} and R_{7a} each independently represent hydrogen or C_1-C_3 alkyl, or

(ii) R_4, R_{4a} and R_5 taken together with the carbon atoms to which they are attached form an optionally substituted benzene or pyridine ring fused to the cyclic amine ring, R_{7a} represents hydrogen or C_1-C_3 alkyl, and R_6 and R_7 each

independently represents a radical of formula (II) as defined in relation to R_2, or

(iii) R_4, R_{4a} and R_5 taken together with the carbon atoms to which they are attached form an optionally substituted benzene or pyridine ring fused to the cyclic amine ring, R_6, R_7 and R_{7a} taken together with the carbon atoms to which they are attached also form an optionally substituted benzene or pyridine ring fused to the cyclic amine ring, or

(iv) when W is a cyclic amino radical of formula (IIIA) wherein Y is -(CH(R_8))-, then R_4, R_{4a} and R_8 taken together with the carbon atoms to which they are attached form an optionally substituted benzene or pyridine ring fused to the cyclic amine ring, R_{7a} represents hydrogen or C_1-C_3 alkyl, and R_5, R_6 and R_7 each independently represents a radical of formula (II) as defined in relation to R_1 and R_2, or

(v) when W is a cyclic amino radical of formula (IIIB) then R_4, R_{4a}, R_7 and R_{7a} taken together with the carbon atoms to which they are attached form an optionally substituted benzene or pyridine ring fused to the cyclic amine ring, and R_5 and R_6 each independently represents a radical of formula (II) as defined in relation to R_1 and R_2,

or a pharmaceutically acceptable salt, hydrate or solvate thereof.

As used herein the term "C_1-C_3alkyl" means a straight or branched chain alkyl moiety having from 1 to 3 carbon atoms, including for example, methyl, ethyl and n-propyl.

As used herein the term "divalent C_1-C_3alkylene radical" means a saturated hydrocarbon chain having from 1 to 3 carbon atoms and two unsatisfied valencies.

As used herein the term "cycloalkyl" means a saturated alicyclic moiety having from 3-8 carbon atoms and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

As used herein the term "cycloalkenyl" means a saturated alicyclic moiety having from 5-8 carbon atoms and at least one double bond, and includes, for example, cyclopentenyl, cyclohexenyl, cycloheptenyl and cyclooctenyl.

As used herein the term "aryl" means a mono-, bi- or tri-cyclic carbocyclic aromatic group, and includes groups consisting of two covalently linked monocyclic carbocyclic aromatic groups. Illustrative of such groups are phenyl, biphenyl and napthyl.

As used herein, the term C_3-C_8 carbocyclic ring means a ring of 3 to 8 carbon atoms, with no heteroatom as part of the ring. The term includes aromatic (aryl) and non aromatic (non aryl) carbocyclic rings, for example the benzene ring and cycloalkyl rings.

As used herein the term "heteroaryl" refers to a 5- or 6- membered aromatic ring containing one or more heteroatoms, and optionally fused to a benzyl or pyridyl ring; and to groups consisting of two covalently linked 5- or 6- membered aromatic rings each containing one or more heteroatoms; and to groups consisting of a monocyclic carbocyclic aromatic group covalently linked to a 5- or 6- membered aromatic rings containing one or more heteroatoms, Illustrative of such groups are thienyl, furyl, pyrrolyl, imidazolyl, benzimidazolyl, thiazolyl, pyrazolyl, isoxazolyl, isothiazolyl, triazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, 4-([1,2,3]-thiadiazoly-4-yl)phenyl and 5-isoxazol-3-ylthienyl.

As used herein the terms "heterocyclic ring having 5 or 6 ring members" "heterocyclyl" or "heterocyclic" includes "heteroaryl" as defined above, and in addition means a 5 or 6 membered aromatic or non-aromatic heterocyclic ring

containing one or more heteroatoms selected from S, N and O, and optionally fused to a benzene ring, including for example, pyrrolyl, furyl, thienyl, piperidinyl, imidazolyl, oxazolyl, thiazolyl, thiadiazolyl, pyrazolyl, pyridinyl, pyrrolidinyl, pyrimidinyl, morpholinyl, piperazinyl, indolyl, benzimidazolyl, maleimido, succinimido, phthalimido and 1,3-dioxo-1,3-dihydro-isoindol-2-yl groups.

Where any group herein is referred to as "optionally substituted" this means the group may be unsubstituted or substituted with at least one substituent selected from (C_1-C_3)alkyl, (C_1-C_3)alkoxy, oxo, phenyl, phenoxy, hydroxy, mercapto, (C_1-C_6)alkylthio, amino, halo (including fluoro, chloro, bromo and iodo), trifluoromethyl, cyano, nitro, -COOH, -$CONH_2$, -$COOR^A$, -$NHCOR^A$, -$CONHR^A$, -NHR^A, -NR^AR^B, or -$CONR^AR^B$ wherein R^A and R^B are independently (C_1-C_3)alkyl.

Salts of the compounds of the invention include physiologically acceptable acid addition salts for example hydrochlorides, hydrobromides, sulphates, methane sulphonates, p-toluenesulphonates, phosphates, acetates, citrates, succinates, lactates, tartrates, fumarates and maleates. Salts may also be formed with bases, for example sodium, potassium, magnesium, and calcium salts.

There are at least two actual or potential chiral centres in the compounds according to the invention because of the presence of asymmetric carbon atoms. The presence of several asymmetric carbon atoms gives rise to a number of diastereomers with R or S stereochemistry at each chiral centre. The invention includes all such diastereomers and mixtures thereof.

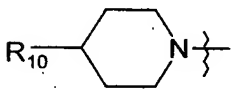
In the compounds of the invention:

X is a carboxylic acid group -COOH, or a hydroxamic acid group -CONHOH;

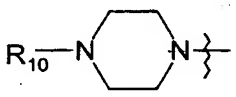
R_1 may be, for example, an optionally substituted C_1-C_6alkyl, phenyl, or phenyl(C_1-C_6alkyl)- group;

R_2 may be, for example hydrogen, or an optionally substituted C_1-C_6alkyl, phenyl(C_1-C_6alkyl)-group, or an optionally substituted heterocyclic group;

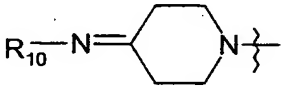
W may be, for example a radical of formula (IIIC), (IIID) or (IIIE)



(IIIC)



(IIID)



(IIIE)

wherein R_{10} is as defined in relation to R_2 in formula (I), for example an optionally substituted phenyl, biphenyl, phenyl(C_1-C_6alkyl)-, phenoxy, phenoxy(C_1-C_3)alkyl, or heterocyclic group;

Thus, examples of compounds of the invention include those wherein

X is a carboxylic acid group -COOH, or a hydroxamic acid group -CONHOH;

R_1 is n-propyl, iso-propyl n-butyl, iso-butyl, benzyl, phenylethyl, 4-fluorobenzyl, or 4-fluorophenylethyl;

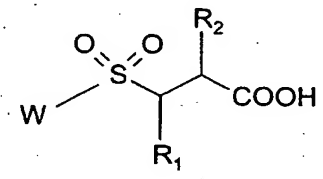
R_2 is hydrogen, n-propyl, n-butyl, iso-butyl, benzyl, phenylethyl, tetrahydropyranyl, 1-(3,4,4-trimethyl-2,5-dioxoimidazolidin-1-yl)propyl, or 1-(phthalimido)-propyl;

W is a radical of formula (IIIC), (IIID), or (IIIE) wherein R_{10} is n-propyl, n-butyl or iso-butyl; or a phenyl, phenoxy, benzyl, phenylethyl, phenylpropyl, phenoxy, or phenoxymethyl group, any of which may be substituted in the phenyl ring, for example in the 4-position, by chloro, fluoro, methoxy or cyano; pyridinyl or pyridinyloxy either of which may be substituted by chloro, fluoro, methoxy or cyano; or biphenyl or 4-pyridinylphenyl, either of which may be substituted in either ring by chloro, fluoro, methoxy or cyano. Examples of W

radicals include 4-phenylmethylpiperidinyl, 4 methylpiperidinyl, 4-(4-methylphenyl)piperidinyl, 4-(4-chlorophenoxy)piperidinyl, 4-phenylpiperidinyl, 4(4-fluorophenyl)piperidinyl, 4-(4-fluorophenoxy)piperidinyl, 4-(4-pyridinyloxy)-piperidinyl, 4-(4-cyanophenyloxy)piperidinyl, 4-(4-cyanophenoxyimino)-piperdinyl, 4-(4'-chloro-biphenyl-4-yl)-piperdinyl, 4-(2-chloro-biphenyl-4-yl) piperdinyl, 4-(4-fluorophenylmethyl)piperidinyl, 4-(4-fluorophenoxymethyl)-piperidinyl, 4-phenylpiperazinyl, 4-(4-fluorophenyl)piperazinyl, 4-(4-pyridinyl-methyl)piperazinyl, 4-(4-chlororophenyl)piperazinyl, 4-pyridin-4-ylpiperazinyl, 4-phenylmethylpiperazinyl, and 4-(4-fluorophenylmethyl)piperazinyl.

Specific examples of compounds in accordance with the invention include those named and characterised in the Examples herein, and pharmaceutically acceptable salts, hydrates or solvates thereof. One interesting compound of the invention is 3-[4-(4-fluoro-phenoxymethyl)-piperidine-1-sulfonyl]-*N*-hydroxy-4-phenyl-butyramide, and its pharmaceutically acceptable salts, hydrates and solvates. This compound is an inhibitor of collagenase-3 (MMP-13), in particular. Another interesting compound of the invention is 3-(4-benzyl-piperidine-1-sulfonyl)-*N*-hydroxy-4-phenyl-butyramide, and its pharmaceutically acceptable salts, hydrates and solvates. This compound is an inhibitor of gelatinase A, in particular.

Compounds of the invention wherein X is a hydroxamic acid group may be prepared by a process which comprises causing a carboxylic acid of the invention of general formula (IV)

(IV) 

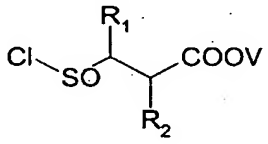
or an activated derivative thereof to react with hydroxylamine, O-protected hydroxylamine, N,O-diprotected hydroxylamine, or a salt thereof, W, R_1 and R_2 being as defined in general formula (I), and subsequently removing any protecting groups from the hydroxylamine moiety

Conversion of (IV) to an activated derivative such as the pentafluorophenyl, hydroxysuccinyl, or hydroxybenzotriazolyl ester may be effected by reaction with the appropriate hydroxy compound in the presence of a dehydrating agent such as dicyclohexyl dicarbodiimide (DCC), N,N-dimethylaminopropyl-N'-ethyl carbodiimide (EDC), or 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ).

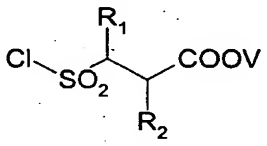
Examples of O-protected hydroxylamines for use in the process of the invention above include O-benzylhydroxylamine, O-4-methoxybenzylhydroxylamine, O-trimethylsilylhydroxylamine, and O-tert-butoxycarbonylhydroxylamine.

Examples of O,N-diprotected hydroxylamines for use in the process of the invention include N,O-bis(benzyl)hydroxylamine, N,O-bis(4-methoxybenzyl)hydroxylamine, N-tert-butoxycarbonyl-O-tert-butyldimethylsilylhydroxylamine, N-tert-butoxycarbonyl-O-tetrahydropyranylhydroxylamine, and N,O-bis(tert-butoxycarbonyl)hydroxylamine.

Carboxylic acids of formula (IV) may be prepared by condensation of a sulfinyl chloride of formula (V) or a sulfonyl chloride of formula (VA)



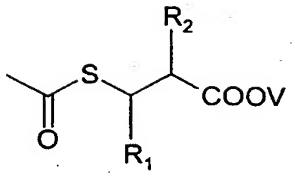
(V)



(VI)

wherein V is a carboxyl protecting group and R_1 and R_2 are as defined with respect to formula (I), with a cyclic amine W-H wherein W is as defined with respect to formula (I) followed, in the case of the sulfinyl chloride (V), by oxidation of the sulfinyl group to a sulfonyl group and, in each case, thereafter removing the protecting group V.

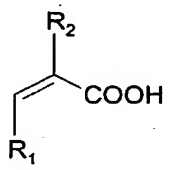
Sulfinyl chlorides of formula (V) may be prepared by reaction of an acetylthio compound of formula (VI)

(VI) 

wherein V is a carboxyl protecting group and R_1 and R_2 are as defined with respect to formula (I), with sulfuryl chloride in the presence of acetic anhydride.

Sulfonyl chlorides of formula (VA) may be prepared by reaction of an acetylthio compound of formula (VI) as defined above, with chlorine and aqueous acetic acid.

Acetylthio compounds of formula (VI) may be prepared by reaction of an α,β-unsaturated carboxylic acid of formula (VII)

(VII) 

wherein R_1 and R_2 are as defined with respect to formula (I),with thiolacetic acid, followed by protection of the carboxylic acid group.

The preparative Examples herein give further details of the reaction conditions for the preparation of compounds of the invention and intermediates there of.

As mentioned above, the compounds of the invention are inhibitors of matrix metalloproteinases and therefore of value in the treatment of disease states or conditions resulting from over production of, or over responsiveness to, MMPs.

Accordingly in another aspect, this invention concerns:

(i) a method of treatment of conditions in mammals, in particular in humans, resulting from over production of or over responsiveness to MMPs, which method comprises administering to the mammal an effective amount of a compound as

defined with respect to formula (I) above; and

(ii) a compound as defined with respect to formula (I) for use in human or veterinary medicine treatment of conditions resulting from over production of or over responsiveness to MMPs; and

(iii) the use of a compound as defined with respect to formula (I) in the preparation of an agent for treatment of conditions in mammals, in particular in humans, resulting from over production of or over responsiveness to MMPs.

Conditions resulting from over production of or over responsiveness to MMPs include rheumatoid arthritis, osteoarthritis, osteopenias such as osteoporosis, periodontitis, gingivitis, corneal. Epidermal, venous, diabetic or gastric ulceration, ulcerative colitis, Crohn's disease, pressure sores, tumour metastasis, invasion and growth, multiple sclerosis, angiogenesis dependent diseases, which include arthritic conditions and solid tumour growth as well as psoriasis, proliferative retinopathies, neovascular glaucoma, ocular tumours, angiofibromas and hemangiomas.

According to a further aspect of the invention there is provided a pharmaceutical or veterinary formulation comprising a compound of general formula (I) and a pharmaceutically and/or veterinarily acceptable carrier. One or more compounds of general formula (I) may be present in association with one or more non-toxic pharmaceutically and/or veterinarily acceptable carriers and/or diluents and/or adjuvants and if desired other active ingredients.

Compositions with which the invention is concerned may be prepared for administration by any route consistent with the pharmacokinetic properties of the active ingredient(s).

Orally administrable compositions may be in the form of tablets, capsules, powders, granules, lozenges, liquid or gel preparations, such as oral, topical, or sterile

parenteral solutions or suspensions. Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinyl-pyrrolidone; fillers for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricant, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants for example potato starch, or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, glucose syrup, gelatin hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

For topical application to the skin, the active ingredient(s) may be made up into a cream, lotion or ointment. Cream or ointment formulations which may be used for the drug are conventional formulations well known in the art, for example as described in standard textbooks of pharmaceutics such as the British Pharmacopoeia.

For treatment of the respiratory tract, the active ingredient(s) may be made up as inhaleable aerosols or sprays in which the compound is dissolved or suspended, or as inhaleable powders, by conventional formulation methods.

The active ingredient(s) may also be administered parenterally in a sterile medium. Depending on the vehicle and concentration used, the drug can either be suspended

or dissolved in the vehicle. Advantageously, adjuvants such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle.

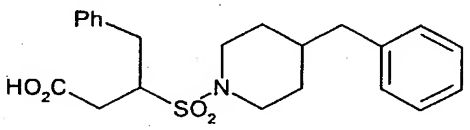
Safe and effective dosages for different classes of patient and for different disease states will be determined by clinical trial as is required in the art. It will be understood that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

The following Examples illustrate embodiments of the invention. The starting α,β-unsaturated acids are either commercially available or may be prepared by known literature methods. In the Examples, the following abbreviations have been used:

DCM	Dichloromethane
DMAP	4-Dimethylaminopyridine
DMF	N,N-Dimethylformamide
EDC	N-Ethyl-N^1-(3-dimethylaminopropyl) carbodiimide hydrochloride
EtOAc	Ethylacetate
EtOH	Ethanol
HOBt	1-Hydroxybenzotriazole
MeOH	Methanol
$NaIO_4$	Sodium periodate
NaOH	Sodium hydroxide
NMM	N-Methyl morpholine
Ph_3PO	Triphenyl phospine oxide
$RuCl_3.xH_2O$	Ruthenium (III) chloride hydrate
TEA	Triethylamine
TFA	Trifluoroacetic acid
TLC	Thin layer chromatography

^1H and ^{13}C NMR spectra were recorded using either a Bruker DPX250 spectrometer at 250.1 and 62.9 MHz respectively, or a Bruker AMX2 500 spectrometer at 500.1 and 125.7 MHz respectively. Mass spectra were obtained on a PE-SCIEX API 165 with a turbo ion spray interface. Infra red spectra were obtained on a Perkin Elmer 1600 series FTIR machine. All organic solutions were dried over $MgSO_4$.

EXAMPLE 1



3-(4-Benzy-piperidine-1-sulfonyl)-4-phenyl-butyric acid.

STEP A:

5-Phenyl-but-2-enoic acid

Tert-butoxycarbonylmethylene triphenyl phosphonium bromide (22.16 g, 48.5 mmol) was suspended in water (100 mL) and DCM (50 mL) and basified with 2M NaOH (against phenolphthalein indicator). The layers were separated and the aqueous layer re-extracted with DCM. The DCM extracts were combined, dried, filtered and evaporated under reduced pressure to give a gummy solid. This was re-suspended in benzene (50 mL) with stirring and cooled to 0 °C. Phenylacetaldehyde (5.76 g, 48 mmol) was added and the reaction warmed to room temperature and stirred overnight. The precipitated Ph_3PO was filtered off and the filtrate concentrated *in vacuo*. The resulting residue was stirred in hexanes and re-filtered. The filtrate was again concentrated under reduced pressure to give 3-(4-Benzy-piperidine-1-sulfonyl)-4-phenyl-butyric acid *tert*-butyl ester as a yellow oil (8.29 g, 38 mmol). This was taken up in DCM with stirring and cooled to 0 °C. TFA (10 mL) was added and

the reaction placed in the fridge overnight. The solvents were evaporated under reduced pressure to give the title compound as a semi-solid (6.66 g, Quant.) ^{1}H-NMR δ ($CDCl_3$) 7.48 - 7.16 (6H, m), 5.79 (1H, d, J=15.6 Hz), 3.55 (2H, d, J=6.7 Hz).

STEP B:

3-Acetylsulfanyl-4-phenyl-butyric acid.

Thiolacetic acid (9.3 mL, 131 mmol) was added to 4-phenyl-but-2-enoic acid (4.25 g, 26.2 mmol) under an argon atmoshere. The resulting solution stirred with the exclusion of light at room temperature for 48 h. The solvent was evaporated to yield an orange oil (6.26 g, Quant). ^{1}H-NMR δ ($CDCl_3$), 7.25 (5H, m), 4.09 (1H, m), 2.99 (2H, d, J=6.4 Hz), 2.66(2H, d, J=6.4 Hz) and 2.30 (3H, s).

STEP C:

3-Acetylsulfanyl-4-phenyl-butyric acid benzyl ester.

The product from Step B (5.4 g, 26.2 mmol) was taken up in DCM (50 mL) with stirring and cooled to 0°C. EDC (6.0 g, 31.4 mmol) and DMAP (164 mg, 1.31 mmol) were added followed by benzyl alcohol (2.4 mL, 23.6 mmol). The resulting solution was stirred at room temperature overnight with the exclusion of moisture. The reaction was diluted with DCM and washed successively with 1M HCl, water, 5% Na_2CO_3 solution, brine and dried, filtered and evaporated to give a dark oil. This was purified by silica gel column chromatography eluting with hexane / ethyl acetate 1:1 to give the product as an orange oil (5.98 g, 70 %). ^{1}H-NMR δ ($CDCl_3$) 7.38 - 7.17 (10H, m); 5.11 (2H, s), 4.08 (1H, m), 2.96 (2H, d, J=6.4 Hz), 2.64 (2H, d, J=6.4 Hz) and 2.27 (3H, s).

STEP D:

3-(4-Benzyl-piperidine-1-sulfinyl)-4-phenyl-butyric acid benzyl ester.

The product from Step C (670 mg, 2.05 mmol) was taken up in dry DCM (5 mL) with stirring and cooled to -15°C under argon atmosphere. Acetic anhydride (193 µL, 2.05 mmol) and sulfuryl chloride (329 µL, 4.1 mmol) were added *via* a syringe. After being stirred for 1h, the mixture was concentrated *in vacuo* at room temperature. The sulfinyl chloride thus obtained was used for coupling without purification. A solution of 4-benzyl piperidine (370 µL, 2.11 mmol) in dry DCM (5 mL) and NMM (232 µL, 2.11 mmol) was added *via* a cannular to a stirred solution of the sulfinyl chloride in dry DCM (10 mL) at 0°C under an argon atmosphere. The mixture was allowed to warm to room temperature and stirred overnight. The solvent was evaporated to give an oil which was purified by silica gel column chromatography eluting with hexane / ethyl acetate 1:1. This gave the product as a mixture of diastereoisomers (430 mg, 44%). ^{1}H-NMR δ ($CDCl_3$) 7.38 - 7.08 (15H, m), 5.05 (2H, m), 3.55 (1H, m), 3.41-3.25 (2H, m), 3.01-2.42 (7H, m), 1.67 (1H, m) and 1.26 (2H, m).

STEP E:

3-(4-Benzyl-piperidine-1-sulfonyl)-4-phenyl-butyric acid benzyl ester.

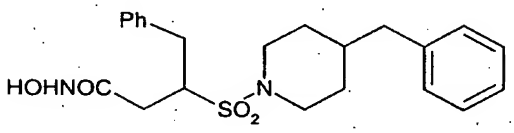
The product from Step D (430 mg, 0.91 mmol) was taken up in acetonitrile (1.5 mL) with stirring and cooled to 0 °C. $RuCl_3.3H_2O$ (0.5 mg) and $NaIO_4$ (290 mg, 1.37 mmol) were added followed by water (2 mL). The resulting mixture was stirred at room temperature for 2½h until tlc (hex/EtOAc 1:1) indicated the absence of starting material. The reaction was diluted with DCM, the layers separated and the aqueous layer was further extracted with DCM. The organic extracts were combined, dried, filtered and concentrated *in vacuo* to give the product as an oil (360 mg, 81%). ^{1}H-NMR δ ($CDCl_3$) 7.37 - 7.09 (15H, m), 4.96 (1H,d, J=12.2Hz), 4.94 (1H, d, J=12.2 Hz), 3.91 (1H, m), 3.89-3.68 (2H, m), 3.31 (1H, dd, J=4.5, 14.0 Hz), 2.88-2.45 (7H, m), 1.72-1.50 (3H, m) and 1.29-1.15 (2H, m)

STEP F:

3-(4-Benzyl-piperidine-1-sulfonyl)-4-phenyl-butyric acid.

The product from Step E (360 mg, 0.73 mmol) was taken up in EtOAc (10 mL) with stirring under a blanket of argon. 10% palladium on charcoal (130 mg) was added. The resulting suspension was hydrogenated in a PARR apparatus at room temperature overnight.The system was purged with argon and the catalyst removed by filtration. The filtrate was evaporated under reduced pressure to give the desired product as a gum (292mg, Quant). ^{1}H-NMR δ(MeOD) 7.24-7.10 (10H, m), 3.89 (1H, m), 3.69 (2H, m), 3.25 (1H, dd, J = 4.8, 17.1 Hz), 2.81-2.64 (4H, m), 2.53 (2H, d, J = 6.7 Hz), 2.45 (1H, dd, J = 4.8, 17.1 Hz), 1.61 (3H, m) and 1.28 (2H, m). ^{13}C-NMR δ(MeOD) 174.3, 141.7, 138.8, 130.8, 130.6, 130.2, 129.7, 128.4, 127.4, 61.0, 47.6, 44.2, 39.2, 36.6, 34.8, 33.7. ESMS = (M+1) 402.2, (M-1) 400.0.

EXAMPLE 2



3-(4-Benzyl-piperidine-1-sulfonyl)-*N*-Hydroxy-4-phenyl-butyramide.

STEP G:

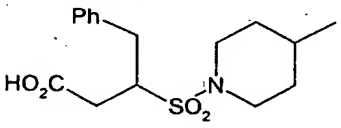
3-(4-Benzyl-piperidine-1-sulfonyl)-*N*-Hydroxy-4-phenyl-butyramide.

The product from Step F (292 mg, 0.73 mmol) was taken up in DMF (5 mL) with stirring and cooled to 0°C and HOBt (124 mg, 0.92 mmol) followed by EDC (176 mg, 0.92 mmol) were added. After 1h at 0°C hydroxylamine hydrochloride (161 mg, 2.31 mmol) and NMM (254 µL, 2.31 mmol) were added. The reaction was allowed to

warm to room temperature and stirred overnight. The solvent was removed *in vacuo* and the residue was purified by reverse phase HPLC to give the desired product as a white solid (21 mg). ^{1}H-NMR δ(MeOD) 7.33-7.11 (10H, m), 4.00 (1H, m), 3.68 (2H, m), 3.23 (1H, dd, J = 4.9, 14.1 Hz), 2.76 (3H, m), 2.51 (3H, m), 2.21 (1H, dd, J - 4.9, 14.1 Hz), 1.63 (3H, m) and 1.20 (2H, m). ^{13}C-NMR δ(MeOD) 169.5, 141.7, 138.9, 130.8, 130.6, 130.2, 129.7, 128.4, 127.4, 60.0, 47.4, 44.2, 39.2, 36.7, 33.6, 33.3. IR ν_{max} (reflection disc) 2921, 1665, 1447, 1309, 1137, 940, 747. ESMS = (M+1) 417.0, (M+TFA-1) 529.2, (M-1) 415.0.

The compounds of Examples 3 to 18 were prepared by modification of the methods described for Examples 1 and 2 as indicated in the text. The starting α,β-unsaturated acids if not commercially available maybe prepared from commercially available aldehydes and ylides as described in Step A. The substituted piperidine derivatives or other amines required are either commercially available or may be prepared by known literature methods (Perregaard, J; Moltzen, E. K; Meier, E; Sanchez, C; *J. Med. Chem.* **1995**, *38*, 1998-2008 and by using the Mitsonobu reaction conditions in Gowravaram, M. R; Tomczuk, B. E; Johnson, J. S; Delecki, D; Cooke, E. R; Ghose, A. K; Mathiowetz, A. M; Spurlino, J. C; Rubin, B; Smith, D. L; Pulvino, T; Wahl, R. C; *J. Med. Chem.* **1995**, *38*, 2570-2581).

EXAMPLE 3



3-(4-Methyl-piperidine-1-sulfonyl)-4-phenyl-butyric acid

STEP H:

3-Chlorosulfonyl-4-phenyl-butyric acid benzyl ester

The product from Step C (1.20 g, 3.66 mmol) was suspended in a 5% acetic acid water solution (50 mL) with stirring and cooled to 0 °C. Chlorine gas was bubbled through this cooled suspension for 15 min. Reaction was stirred at 0 °C was a further 20 min and then the excess chlorine was removed by bubbling argon through the suspension. the product was extracted into DCM. The DCM extract was was washed with water (X3), brine (X3), dried, filtered and evaporated *in vacuo* to give the title compound as a yellow oil (0.92 g, 2.6 mmol). ^{1}H-NMR δ ($CDCl_3$) 7.42 - 7.20 (10H, m), 4.98 (2H,s), 4.45 (1H, m), 3.62 (1H, dd, J=4.4, 14.1 Hz), 3.12 (1H, dd, J=5.9, 17.1 Hz), 3.00 (1H, dd, J=10, 14.1Hz) and 2.73 (1H, dd, J=6.2, 17.1 Hz)

STEP I:

3-(4-Methyl-piperidine-1-sulfonyl)-4-phenyl-butyric acid benzyl ester

The product from Step H (0.92 g, 2.6 mmol) was taken up in DCM (25 mL) with stirring and cooled to 0 °C. TEA (362 µL, 2.6 mmol) and 4-methyl-piperidine (307 µL, 2.6 mmol) were added and the reaction warmed to room temperature and stiired overnight. The reaction was diluted with DCM and washed successively with water, 1M HCl, water, brine, dried, filtered and concentrated *in vacuo* to give a yellow oil. This was purified by silica gel column chromatography eluting with hex /EtOAc 8:2 to give the titled compound as a yellow oil (440 mg, 41%). ^{1}H-NMR δ ($CDCl_3$) 7.40-7.18 (10H, m), 5.0 (1H, d, J=12.2 Hz), 4.95 (1H, d, J=12.2 Hz), 3.9 (1H, m), 3.79-3.68 (2H, m), 3.42-3.31 (1H, dd, J=4.4, 14.1 Hz), 2.91-2.80 (1H, dd, J=5.9, 17.1 Hz), 2.79-2.62 (3H, m), 2.58-2.47 (1H, dd, J=6.2, 17.1 Hz), 1.69-135 (2H, m), 1.30-1.10 (3H, m) and (3H, d, J=6.2 Hz).

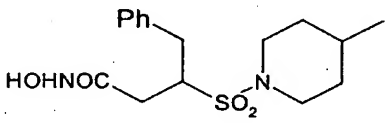
STEP J:

3-(4-Methyl-piperidine-1-sulfonyl)-4-phenyl-butyric acid

The product from Step I (440 mg, 1.06 mmol) was converted to the title compound

using the method in Step F using MeOH (10 mL) as the reaction solvent. Oil (270 mg, 78%). 'H-NMR δ(MeOD) 7.29 (5H, m), 3.88 (1H, m), 3.67 (2H, m), 3.23 (1H, dd, J = 4.3, 12.8 Hz), 2.84 (4H, m), 2.45 (1H, dd, J = 4.3, 12.8 Hz), 1.63 (2H, m), 1.47 (1H, m), 1.17 (2H, m) and 0.93 (3H, d, J = 6.4 Hz). ^{13}C-NMR δ(MeOD) 174.2, 138.8, 130.8, 130.2, 128.4, 61.0, 47.6, 36.6, 35.7, 34.7, 32.0, 22.5. ESMS = (M+Na) 348.2, (M-1) 323.8.

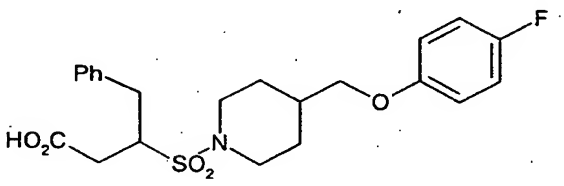
EXAMPLE 4



N-Hydroxy-3-(4-Methylpiperidine-1-sulfonyl)-4-phenyl-butyramide.

The product from Step J (270 mg, 0.83 mmol) was converted to the title compound using the method in Step G to give the title compound as a pink gum (129 mg). 'H-NMR δ(MeOD) 7.31 (5H, m), 3.97 (1H, m), 3.63 (2H, m), 3.24 (1H, dd, J = 4.9, 14.2 Hz), 2.79 (3H, m), 2.51 (1H, dd, J = 7.5, 15.6 Hz), 2.26 (1H, dd, J = 4.9, 14.2 Hz), 1.60 (2H, m), 1.46 (1H, m), 1.14 (2H, m) and 0.92 (3H, d, J = 6.39 Hz). ^{13}C-NMR δ(MeOD) 169.5, 138.9, 130.7, 130.1, 128.4, 59.9, 47.4, 36.7, 35.7, 33.3, 32.0, 22.5. ESMS = (M+Na) 363.0, (M-1) 338.8.

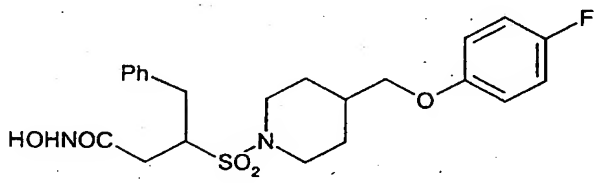
EXAMPLE 5



3-[4-(4-Fluoro-phenoxymethyl)-piperidine-1-sulfonyl]-4-phenyl-butyric acid

Pink gum. ^{1}H-NMR δ(MeOD) 7.35-7.20 (5H, m), 7.12-6.84 (4H, m), 3.91 (1H, m), 3.79-3.76 (4H, m), 3.31 (1H, m), 2.90-2.66 (4H, m), 2.49-2.41 (1H, dd, J = 4.4, 17.2 Hz), 2.0-1.70 (3H, m) and 1.43-1.22 (2H, m). ^{13}C-NMR δ(MeOD) 174.3, 160.9, 157.1, 138.8, 130.8, 130.2, 128.5, 117.2, 117.1, 116.9, 116.8, 74.2, 61.1, 47.2, 37.3, 36.6, 34.8, 30.5. IR ν_{max} (reflection disc) 2947, 1730, 1598, 1503, 1409, 1253, 1054, 1030, 948, 829, 699. ESMS = (M+1) 436.0, (M+TFA-1) 548.0, (M-1) 433.8.

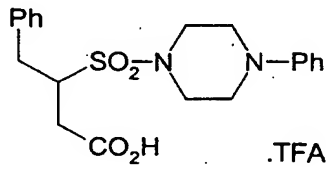
EXAMPLE 6



3-[4-(4-Fluoro-phenoxymethyl)-piperidine-1-sulfonyl]-*N*-hydroxy-4-phenyl-butyramide

Pale pink foam. ^{1}H-NMR δ(MeOD) 7.40-7.26 (5H, m), 7.01-6.84 (4H, m), 4.13 (1H, m), 3.78-3.72 (4H, m), 3.24 (1H, m), 2.81-2.74 (3H, m), 2.59-2.50 (1H, dd, J = 7.6, 15.7 Hz), 2.30-2.22 (1H, dd, J = 4.4, 15.7 Hz), 2.02-1.80 (3H, m) and 1.47-1.20 (2H, m). ^{13}C-NMR δ(MeOD) 169.5, 160.9, 157.1, 138.9, 130.7, 130.2, 128.4, 117.2, 117.1, 117.0, 116.8, 74.2, 60.0, 47.0, 37.3, 36.6, 33.3, 30.5. IR ν_{max} (reflection disc) 3293, 2919, 1664, 1503, 1449, 1307, 1208, 1136, 1044, 937, 828, 751. ESMS = (M+Na) 473.2, (M+TFA-1) 563.2.

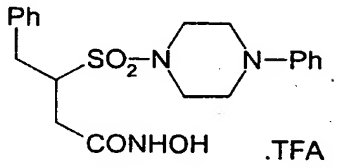
EXAMPLE 7



4-Phenyl-3-(4-phenyl-piperazine-1-sulfonyl)-butyric acid; compound with trifluoro-acetic acid.

Pale pink foam. 'H-NMR δ(MeOD) 7.50-7.20 (7H, m), 7.20-6.99 (3H, m), 4.01 (1H, m), 3.50 (4H, m), 3.40-3.20 (5H, m), 2.89-2.80 (1H, dd, J = 7.3, 17.2 Hz), 2.80-2.71 (1H, dd, J = 7.3, 17.2 Hz) and 2.54-2.46 (1H, dd, J = 4.3, 17.2 Hz). ^{13}C-NMR δ(MeOD) 174.2, 150.2, 138.7, 131.0, 130.8, 130.3, 128.6, 124.7, 119.6, 61.2, 52.8, 46.7, 36.4, 34.8. IR ν_{max} (reflection disc) 3030, 1726, 1661, 1494, 1442, 1324, 1267, 1143, 942. ESMS = (M+1) 388.8, (M-1) 387.0.

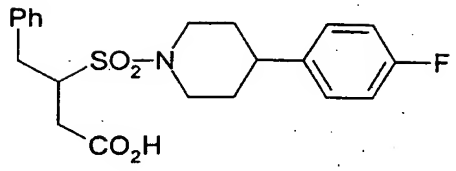
EXAMPLE 8



N-Hydroxy-4-phenyl-3-(4-phenyl-piperazine-1-sulfonyl)-butyramide; compound with trifluoro-acetic acid.

Pink foam. 'H-NMR δ(MeOD) 7.33-7.23 (7H, m), 7.10-6.96 (3H, m), 4.09 (1H, m), 3.42-3.36 (5H, m), 3.29 (4H, m), 2.88-2.78 (1H, dd, J = 8, 16 Hz), 2.62-2.52 (1H, dd, J = 8, 16 Hz) and 2.33-2.25 (1H, dd, J = 4.3, 16 Hz). ^{13}C-NMR δ(MeOD) 169.6, 150.2, 138.7, 131.0, 130.8, 130.3, 128.6, 124.9, 119.7, 60.1, 52.8, 46.8, 36.3, 33.3. IR ν_{max} (reflection disc) 3189, 1668, 1493, 1446, 1143, 945. ESMS = (M+1) 404.0, (M-1) 402.0.

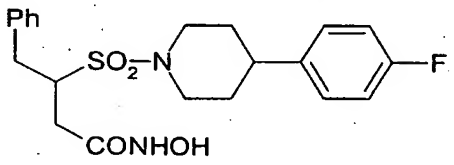
EXAMPLE 9



3-[4-(4-Fluoro-phenyl)-piperidine-1-sulfonyl]-4-phenyl-butyric acid

White solid. 'H-NMR δ(MeOD) 7.45-7.19 (7H, m), 7.03-6.97 (2H, m), 3.99 (1H, m), 3.87-3.81 (2H, bm), 3.37 (1H, m), 3.0-2.60 (5H, m), 2.50 (1H, dd, J = 4.1, 17.2 Hz), 1.90-1.79 (2H, m) and 1.73-1.56 (2H, m). ^{13}C-NMR δ(MeOD) 174.3, 165.2, 161.4, 143.1, 138.8, 130.8, 130.2, 130.0, 129.8, 128.5, 116.6, 116.3, 61.0, 47.9, 42.9, 36.6, 35.0, 34.9. ESMS = (M+Na) 428.2, (M-1) 404.0.

EXAMPLE 10

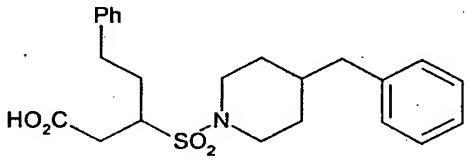


3-[4-(4-Fluoro-phenyl)-piperidine-1-sulfonyl]-*N*-hydroxy-4-phenyl-butyramide

White solid. 'H-NMR δ(MeOD) 7.40-7.20 (7H, m), 7.22-6.96 (2H, m), 4.05 (1H, m), 3.81-3.77 (2H, bm), 3.30 (1H, m), 3.02-2.85 (3H, bm), 2.77-2.55 (2H, bm), 2.30-2.34 (1H, bdd), 1.90-1.80 (2H, m) and 1.75-1.55 (2H, m). ^{13}C-NMR δ(MeOD) 169.5, 165.2, 161.4, 143.2, 139.0, 130.8, 130.2, 130.0, 129.9, 128.4, 116.6, 116.2, 59.9, 47.7, 47.6, 43.0, 36.6, 35.0, 34.9, 33.4. IR ν_{max} (ATR) 2922, 1653, 1508, 1448, 1306, 1218, 1134, 1050, 939, 823, 739, 699. ESMS = (M+Na) 443.0, (M+TFA-1) 533.2, (M-1) 418.8.

In examples 11-18 a *tert*-butyl ester was used in place of the benzyl ester (Step C). The method for its preparation is described (Step K) and Step L replaces Step F.

EXAMPLE 11



3-(4-Benzy-piperidine-1-sulfonyl)-5-phenyl-pentanoic acid

STEP K:

3-Acetylsulfanyl-5-phenyl-pentanoic acid *tert*-butyl ester

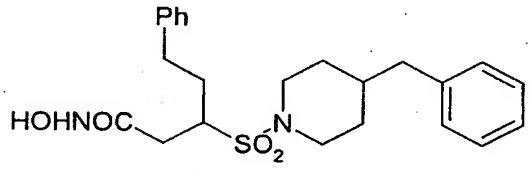
3-Acetylsulfanyl-5-phenyl-pentanoic acid was taken up in DCM (15 mL) with stirring in a pressure bottle. *c.*H_2SO_4 (1 mL) was added and the solution cooled to - 78 °C. Isobutylene gas was bubbled through this solution until the volume had doubled. The pressure vessel was sealed and allowed to warm to room temperature and stirred overnight. The reaction was re-cooled to -78 °C and opened and warmed to room temparature. The excess isobuylene gas was allowed to evaporate and then the reaction solution was poured into a stirred 1M Na_2CO_3 solution. The product was extracted into DCM and washed with brine, dried and filtered and evaporated under reduced pressure to give an orange oil (10.64 g, 34.5 mmol). ^{1}H-NMR δ ($CDCl_3$) 7.27-7.14 (5H, m), 3.88 (1H, m), 2.80-2.51 (4H, m), 2.34 (3H, s), 1.97-1.84 (2H, m) and 1.43 (9H, s).

STEP L;

3-(4-Benzy-piperidine-1-sulfonyl)-5-phenyl-pentanoic acid

3-(4-Benzy-piperidine-1-sulfonyl)-5-phenyl-pentanoic acid *tert*-butyl ester (1.04 g, 2.2 mmol) was taken up in DCM (5 mL) with stirring and cooled to 0 °C. TFA (5 mL) was added slowly and the resulting solution placed in the fridge overnight. Solvents evaporated under reduced pressure to give the title compound as a yellow oil (913 mg, Quant). ^{1}H-NMR δ(MeOD) 7.56-7.11 (10H, m), 3.66-3.56 (3H, m), 2.90-2.59 (6H, m), 2.51 (2H, d, J=6.7 Hz), 2.20 (1H, m), 1.90 (1H, m), 1.62-1.47 (3H, m) and 1.25-1.11 (2H, m). ^{13}C-NMR δ(MeOD) 174.5, 142.6, 141.7, 130.6, 130.1, 130.0, 129.7, 127.7, 127.4, 58.7, 47.6, 44.2, 39.2, 35.5, 33.9, 33.7, 33.0. IR ν_{max} (ATR) 2915, 1709, 1451, 1304, 1133, 1041, 937, 746, 698. ESMS = (M+1) 416.0, (M-1) 414.0.

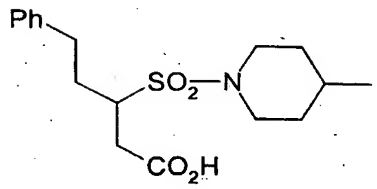
EXAMPLE 12



3-(4-Benzy-piperidine-1-sulfonyl)-5-phenyl-pentanoic acid hydroxyamide

Off-white foam. ^{1}H-NMR δ(MeOD) 7.40-7.13 (10H, m), 3.66-3.50 (3H, m), 2.88-2.58 (5H, m), 2.52 (2H, d, J=6.7 Hz), 2.39 (1H, dd, J = 6.7, 15.3 Hz), 2.10 (1H, m), 1.89 (1H, m), 1.79-1.47 (3H, m) and 1.22-1.08 (2H, m). ^{13}C-NMR δ(MeOD) 169.6, 142.8, 141.7, 130.6, 130.1, 130.0, 129.7, 127.7, 127.4, 58.1, 47.6, 44.2, 39.2, 34.2, 33.9, 33.7, 33.1. IR ν_{max} (ATR) 2917, 1655, 1451, 1303, 1134, 1042, 937, 746, 698. ESMS = (M+1) 431.2, (M-1) 429.0, (M+TFA-1) 543.0.

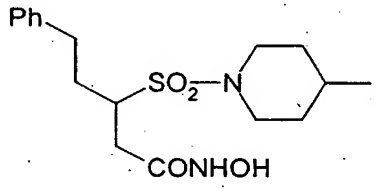
EXAMPLE 13



3-(4-Methyl-piperidine-1-sulfonyl)-5-phenyl-pentanoic acid

Tan solid. ^{1}H-NMR δ(MeOD) 7.51-7.15 (5H, m), 3.80-3.51 (3H, m), 2.95-2.60 (6H, m), 2.17 (1H, m), 1.90 (1H, m), 1.81-1.61 (2H, m), 1.45 (1H, m), 1.30-0.99 (2H, m), 0.92 (3H, d, J = 6.5 Hz). ^{13}C-NMR δ(MeOD) 174.5, 142.6, 130.0, 127.7, 58.7, 47.7, 35.7, 35.5, 33.9, 33.0, 32.1, 22.5. IR ν_{max} (ATR) 2924, 2866, 1710, 1453, 1301, 1161, 1132, 1049, 927, 747, 699. ESMS = (M+Na) 362.2, (M-1) 338.2.

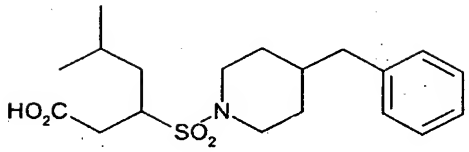
EXAMPLE 14



3-(4-Methyl-piperidine-1-sulfonyl)-5-phenyl-pentanoic acid hydroxyamide

Yellow oil. ^{1}H-NMR δ(MeOD) 7.31-7.17 (5H, m), 3.70-3.61 (3H, m), 2.88-2.61 (5H, m), 2.40 (1H, dd, J = 6.9, 15.3 Hz), 2.13 (1H, m), 1.89 (1H, m), 1.66-1.56 (2H, m), 1.48 (1H, m), 1.22-1.03 (2H, m) and 0.93 (3H, d, J = 6.5 Hz). ^{13}C-NMR δ(MeOD) 169.5, 142.8, 130.0, 127.7, 58.1, 47.6, 35.7, 34.2, 33.9, 33.1, 32.1, 22.5. IR ν_{max} (ATR) 2922, 1655, 1438, 1302, 1161, 1134, 1049, 928, 747, 695. ESMS = (M+Na) 377.2, (M-1) 353.2.

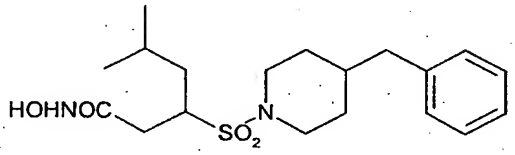
Example 15



3-(4-Benzyl-piperidine-1-sulfonyl)-5-methyl-hexanoic acid

Yellow oil. 'H-NMR δ(MeOD) 7.45-7.13 (5H, m), 3.84-3.60 (2H, m), 3.59 (1H, m), 2.91-2.72 (2H, m), 2.68-2.46 (4H, m), 1.82-1.63 (5H, m), 1.50 (1H, m), 1.39-1.03 (2H, m), 0.96 (3H, d, J=6.2 Hz) and 0.91 (3H, d, J=6.2 Hz). ^{13}C-NMR δ(MeOD) 174.6, 141.7, 130.5, 129.7, 127.5, 58.2, 47.9, 47.7, 44.2, 39.8, 39.3, 35.9, 33.7, 27.0, 23.9, 22.3. IR ν_{max} (ATR) 2924, 1709, 1449, 1320, 1128, 1042, 937, 747, 699. ESMS = (M+Na) 390.0, (M-1) 366.0.

EXAMPLE 16

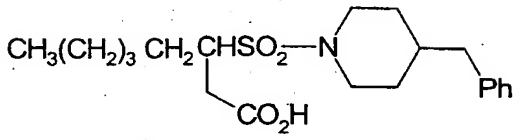


3-(4-Benzyl-piperidine-1-sulfonyl)-5-methyl-hexanoic acid hydroxyamide

Off-white foam. 'H-NMR δ(MeOD) 7.28-7.13 (15H, m), 3.72-3.59 (3H, m), 2.84-2.75 (2H, m), 2.69-2.59 (3H, m), 2.24 (1H, dd, J = 6.1, 15.6 Hz), 1.79-1.64 (5H, m), 1.45 (1H, m), 1.36-1.12 (2H, m) 0.94 (3H, d, J=6.3 Hz) and 0.91 (3H, d, J=6.3 Hz). ^{13}C-NMR δ(MeOD) 169.5, 141.7, 130.6, 129.7, 127.4, 57.4, 47.8, 47.6, 44.2, 40.0, 39.7, 34.7, 33.8, 27.0, 23.8, 22.5. IR ν_{max} (ATR) 2927, 1657, 1451, 1320, 1130, 1042,

940, 746, 699. ESMS = (M+Na) 405.0, (M-1) 381.0.

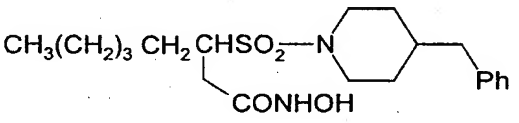
EXAMPLE 17



3-(4-Benzyl-piperidine-1-sulfonyl)-octanoic acid

Yellow oil. 'H-NMR δ(MeOD) 7.44-7.13 (5H, m), 3.73-3.68 (2H, m), 3.52 (1H, m), 2.90-2.77 (3H, m), 2.75-2.48 (3H, m), 2.0-1.80 (1H, m), 1.80-1.17 (12H, m) and 0.91 (3H, t, J = 6.7 Hz). ^{13}C-NMR δ(MeOD) 174.6, 141.7, 130.6, 129.7, 127.4, 59.7, 47.9, 47.6, 44.2, 39.3, 35.5, 33.7, 33.1, 30.8, 27.6, 23.8, 14.7. IR ν_{max} (ATR) 2923, 2853, 1709, 1451, 1304, 1135, 1042, 937, 746, 699. ESMS = (M+1) 382.0, (M-1) 379.8.

EXAMPLE 18



3-(4-Benzyl-piperidine-1-sulfonyl)-octanoic acid hydroxyamide

Yellow oil. 'H-NMR δ(MeOD) 7.28-7.13 (5H, m), 3.72-3.67 (2H, m), 3.62-3.52 (1H, m), 2.96-2.76 (2H, m), 2.60-2.51 (3H, m), 2.32 (1H, dd, J = 6.7, 15.4 Hz), 1.92-1.69 (1H, m), 1.69-1.18 (12H, m) and 0.91 (3H, t, J = 6.7 Hz). ^{13}C-NMR δ(MeOD) 169.7, 141.7, 130.6, 129.7, 127.4, 58.9, 47.8, 47.5, 44.2, 39.3, 34.1, 33.8, 33.2, 30.8, 27.6, 23.8, 14.7. IR ν_{max} (ATR) 2923, 2854, 1656, 1452, 1304, 1137, 1042, 938, 746, 699. ESMS = (M+1) 397.2, (M-1) 395.0, (M+TFA-1) 509.0.

In Vitro MMP Assay and Inhibitor IC_{50} Determination

The potency of compounds of the invention as inhibitors of collagenase may be determined by the procedure of Cawston and Barrett, (Anal. Biochem., **99**, 340-345, 1979), whereby a 1mM solution of the compound being tested, or a dilution thereof, is incubated at 37° for 16 hours with collagen and collagenase (buffered with 25mM Hepes, pH 7.5 containing 5mM $CaCl_2$, 0.05% Brij 35 and 0.02% NaN_3). The collagen is acetylated ^{14}C collagen prepared by the method of Cawston and Murphy, (Methods in Enzymology, **80**, 711, 1981). The samples are centrifuged to sediment undigested collagen, and an aliquot of the radioactive supernatant removed for assay on a scintillation counter as a measure of hydrolysis. The collagenase activity in the presence of 1mM of the test compound, or a dilution thereof, is compared to activity in a control devoid of inhibitor and the result reported as that of inhibitor concentration effecting 50% inhibition of the collagenase activity (IC_{50}).

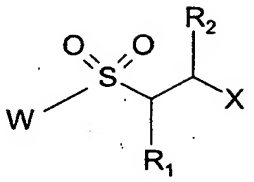
The potency of compounds of the invention as inhibitors of stromelysin may be determined by the procedure of Cawston et al, (Biochem. J., **195**, 159-165, 1981), whereby a 1mM solution of the compound being tested, or a dilution thereof, is incubated at 37° for 16 hours with stromelysin and ^{14}C acetylate casein (buffered with 25mM Hepes, pH 7.5 containing 5mM $CaCl_2$, 0.05% Brij 35 and 0.02% NaN_3). The casein is acetylated ^{14}C casein prepared by the method of Cawston et al (ibid). The stromelysin activity in the presence of 1mM of the test compound, or a dilution thereof, is compared to activity in a control devoid of inhibitor and the result reported as that of inhibitor concentration effecting 50% inhibition of the stromelysin activity (IC_{50}).

The potency of compounds of the invention as inhibitors of 72 kDa gelatinase may be determined by a procedure based on the method of Sellers et. al, Biochem. J., **171**, 493-496 (1979). 72 kDa gelatinase, derived from RPMI-7951 cells is purified by gelatin-agarose chromatography. The enzyme is activated by incubation with aminophenyl mercuric acetate and approximately 0.05 units is incubated with 50μg

[^{14}C]-radiolabellet gelatin in an appropriate buffer for 16 hours at 37°C. At the end of the incubation 50μg bovine serum albumin, together with trichloroacetic acid (final concentration 16%) are added to stop the reaction and to precipitate any undegraded substrate. The reaction tubes are placed on ice for 15 minutes before centrifugation at 10,000g for 15 minutes to sediment the precipitated substrate. A 200μl aliquot of the reaction supernatant is removed and the radioactivity determined by liquid scintillation counting. The effect of the inhibitors is determined by reference to a dose response curve. The IC_{50} (the concentration of inhibitor required to cause a 50% decrease in enzyme activity) is obtained by fitting a curve to the data and computing the concentration of inhibitor required to achieve 50% inhibition of the enzyme. For each IC_{50} determination, the effect on gelatinase activity of at least 8 concentrations of the inhibitor are examined. The inhibitors are dissolved and diluted in DMSO.

Claims

1. A compound of formula (I)

(I) 

wherein

X represents a carboxylic acid group -COOH, or a hydroxamic acid group -CONHOH;

R_2 represents a radical of formula (II)

$$R_3\text{-}(ALK)_m\text{-}(Q)_p\text{-}(ALK)_n\text{-} \qquad (II)$$

wherein

R_3 represents hydrogen or an optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted aryl, or optionally substituted heterocyclic ring having 5 or 6 ring members,

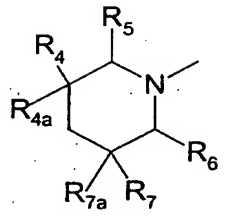
each ALK independently represents an optionally substituted divalent C_1-C_3 alkylene radical,

Q represents -O-, -S-, -S(O)-, -S(O_2)-, -C(O)O-, -OC(O)- or -N(R_9)- wherein R_9 is hydrogen, C_1-C_6alkyl, or C_1-C_6alkoxy, and

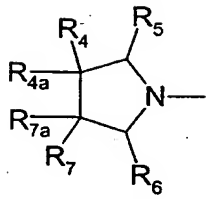
m, n and p are independently 0 or 1;

R_1 represents a radical of formula (II) as defined for R_2, except that R_1 is not hydrogen;

W represents a cyclic amino radical of formula (IIIA) or (IIIB):



(IIIA)



(IIIB)

wherein

Y represents -O-, -S-, -S(O)-, -S(O_2)-, -N(R_8)-, -(CH(R_8))-, or -(C=N-R_8)- wherein R_8 is a radical of formula (II) as defined in relation to R_2; and

(i) R_4, R_5, R_6 and R_7 each independently represents a radical of formula (II) as defined in relation to R_2, and R_{4a} and R_{7a} each independently represent hydrogen or C_1-C_3 alkyl, or

(ii) R_4, R_{4a} and R_5 taken together with the carbon atoms to which they are attached form an optionally substituted benzene or pyridine ring fused to the cyclic amine ring, R_{7a} represents hydrogen or C_1-C_3 alkyl, and R_6 and R_7 each independently represents a radical of formula (II) as defined in relation to R_2, or

(iii) R_4, R_{4a} and R_5 taken together with the carbon atoms to which they are attached form an optionally substituted benzene or pyridine ring fused to the cyclic amine ring, R_6, R_7 and R_{7a} taken together with the carbon atoms to which they are attached also form an optionally substituted benzene or pyridine ring fused to the cyclic amine ring, or

(iv) when W is a cyclic amino radical of formula (IIIA) wherein Y is -(CH(R_8))-, then R_4, R_{4a} and R_8 taken together with the carbon atoms to which they are attached form an optionally substituted benzene or pyridine ring fused to the cyclic amine ring, R_{7a} represents hydrogen or C_1-C_3 alkyl, and R_5, R_6 and R_7

each independently represents a radical of formula (II) as defined in relation to R_1 and R_2, or

(v) when W is a cyclic amino radical of formula (IIIB) then R_4, R_{4a}, R_7 and R_{7a} taken together with the carbon atoms to which they are attached form an optionally substituted benzene or pyridine ring fused to the cyclic amine ring, and R_5 and R_6 each independently represents a radical of formula (II) as defined in relation to R_1 and R_2,

or a pharmaceutically acceptable salt, hydrate or solvate thereof.

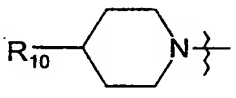
2. A compound as claimed in claim 1 wherein R_1 is an optionally substituted C_1-C_6alkyl, phenyl, or phenyl(C_1-C_6alkyl)- group.

3. A compound as claimed in claim 3 wherein R_1 is n-propyl, iso-propyl n-butyl, iso-butyl, benzyl, phenylethyl, 4-fluorobenzyl, or 4-fluorophenylethyl.

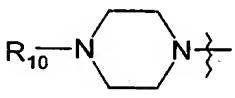
4. A compound as claimed in any preceding claim wherein R_2 is hydrogen, or an optionally substituted C_1-C_6alkyl, phenyl(C_1-C_6alkyl)-group, or an optionally substituted heterocyclic group.

5. A compound as claimed in claim 4 wherein R_2 is hydrogen, n-propyl, n-butyl, iso-butyl, benzyl, phenylethyl, tetrahydropyranyl, 1-(3,4;4-trimethyl-2,5-dioxoimidazolidin-1-yl)propyl, or 1-(phthalimido)-propyl;

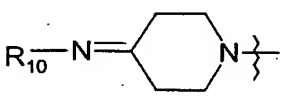
6. A compound as claimed in any preceding claim wherein W is a radical of formula (IIIC), (IIID) or (IIIE)



(IIIC)



(IIID)



(IIIE)

wherein R_{10} is as defined for R_2 in claim 1.

7. A compound as claimed in claim 6 wherein R_{10} is an optionally substituted phenyl, biphenyl, phenyl(C_1-C_6alkyl)-, phenoxy, phenoxy(C_1-C_3)alkyl, or heterocyclic group.

8. A compound as claimed in claim 6 wherein R_{10} is n-propyl, n-butyl or iso-butyl; or a phenyl, phenoxy, benzyl, phenylethyl, phenylpropyl, phenoxy, or phenoxymethyl group, any of which may be substituted in the phenyl ring, for example in the 4-position, by chloro, fluoro, methoxy or cyano; pyridinyl or pyridinyloxy either of which may be substituted by chloro, fluoro, methoxy or cyano; or biphenyl or 4-pyridinylphenyl, either of which may be substituted in either ring by chloro, fluoro, methoxy or cyano.

9. A compound as claimed in claim 6 wherein W is 4-phenylmethylpiperidinyl, 4-methylpiperidinyl, 4-(4-methylphenyl)piperidinyl, 4-(4-chlorophenoxy)piperidinyl, 4-phenylpiperidinyl, 4(4-fluorophenyl)piperidinyl, 4-(4-fluorophenoxy)piperidinyl, 4-(4-pyridinyloxy)-piperidinyl, 4-(4-cyanophenyloxy)piperidinyl, 4-(4-cyanophenoxyimino)-piperdinyl, 4-(4'-chloro-biphenyl-4-yl)-piperdinyl, 4-(2-chloro-biphenyl-4-yl) piperdinyl, 4-(4-fluorophenylmethyl)piperidinyl, 4-(4-fluorophenoxymethyl)-piperidinyl, 4-phenylpiperazinyl, 4-(4-fluorophenyl)piperazinyl, 4-(4-pyridinyl-methyl)piperazinyl, 4-(4-chlororophenyl)piperazinyl, 4-pyridin-4-ylpiperazinyl, 4-phenylmethylpiperazinyl, or 4-(4-fluorophenylmethyl)piperazinyl.

10. 3-[4-(4-Fluoro-phenoxymethyl)-piperidine-1-sulfonyl]-*N*-hydroxy-4-phenyl-butyramide or a pharmaceutically acceptable salt, hydrate or solvate thereof.

11. 3-(4-Benzyl-piperidine-1-sulfonyl)-*N*-hydroxy-4-phenyl-butyramide or a pharmaceutically acceptable salt, hydrate or solvate thereof.

12. A compound as claimed in claim 1 which is specifically named and

characterised in any of Examples 1, 3-5, or 7-18 herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof.

13 A pharmaceutical composition comprising a compound as claimed in any of the preceding claims, together with a pharmaceutically acceptable carrier.

14 A method of treatment of diseases in mammals, in particular in humans, resulting from over production of, or over responsiveness to, MMPs, which method comprises administering to the mammal an effective amount of a compound as claimed in any of claims 1 to 12

15 A compound as claimed in any of claims 1 to 12 or use in human or veterinary medicine treatment of conditions resulting from over production of, or over responsiveness to, MMPs.

16 The use of a compound as claimed in any of claims 1 to 12 in the preparation of an agent for treatment of conditions in mammals, in particular in humans, resulting from over production of, or over responsiveness to, MMPs.

17. A method as claimed in claim 14, or the use as claimed in claim 16 wherein the disease or condition is rheumatoid arthritis, osteoarthritis, osteoporosis, periodontitis, gingivitis, corneal epidermal venous, diabetic or gastric ulceration, ulcerative colitis, Crohn's disease, pressure sores, tumour metastasis, invasion or growth, neuroinflammatory disorder, multiple sclerosis, psoriasis, proliferative retinopathies, neovascular glaucoma, ocular tumours, angiofibromas, hemangiomas, cardiac or cerebral infarction, or wound healing.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 99/02826

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D211/96 C07D295/22 A61K31/445 A61K31/495

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 05635 A (CHIROSCIENCE LTD) 12 February 1998 (1998-02-12) claim 1; example 90	1,13-17
A	DECICCO C P ET AL: "AMIDE SURROGATES OF MATRIX METALLOPROTEINASE INHIBITORS: UREA AND SULFONAMIDE MIMICS" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 7, no. 18, 1 January 1997 (1997-01-01), pages 2331-2336, XP002071089 ISSN: 0960-894X the whole document	1,13-17
P,X	WO 99 24399 A (DARWIN DISCOVERY LTD) 20 May 1999 (1999-05-20) cited in the application claim 1; examples	1,13-17

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 October 1999	09/11/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	De Jong, B

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

ernational application No.
PCT/GB 99/02826

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 14,17
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 14 and 17 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 99/02826

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9805635 A	12-02-1998	AU 3856497 A	25-02-1998
		CZ 9900368 A	14-07-1999
		NO 990543 A	06-04-1999
		PL 331598 A	02-08-1999
		ZA 9707044 A	07-08-1998
WO 9924399 A	20-05-1999	AU 1046999 A	31-05-1999